CLEAN VERSION INCLUDING AMENDMENTS TO THE SPECIFICATION AND CLAIMS

In the specification:

Please insert pages 1-20 of the enclosed sequence listing after the claims.

Please replace the following paragraphs with the clean versions provided hereinbelow:

At page 11, lines 4-9:

--For example, in one aspect, the lipophile and hydrophile are connected by hydrolyzable bonds. It is preferred to provide hydrolyzable bonds between the fatty acid and the hydrophilic moieties. This permits hydrolysis to occur after penetration into the CNS, thus releasing the active peptides with the hydrophilic group still attached to the peptide. As a result, the peptide acquires a more hydrophilic character and efflux to the circulatory system is thereby hindered.--

At page 11, line 19:

--DHA MET-ENKEPHALIN-LYS (**SEQ ID NO:1**)--

At page 11, lines 25-29:

H_2N-Tyr-Gly-Gly-Phe-Met-Lys-COOH
|
HN— C(O)-OC_2H_4-OC_2H_4-N-C(O)$(CH_2)_7$-CH=CH-CH_2-CH=CH-$(CH_2)_4$-CH_3

LINOLEIC MET-ENKEPHALIN-LYS (**SEQ ID NO:1**)--

At page 11, line 40:

--CETYL MET-ENKEPHALIN-LYS (**SEQ ID NO:1**)--

At page 12, line 16:

--CHOLESTEROL MET-ENKEPHALIN-LYS (**SEQ ID NO:1**)--

At page 12, line 29:

--PALMITATE MET-ENKEPHALIN-LYS (**SEQ ID NO:1**)--

At page 12, line 44:

--DI-PALMITATE-TEG MET-ENKEPHALIN-LYS (**SEQ ID NO:2**)--

At page 13, lines 14-15:

--For the enkephalin analogues, the preferred peptides are leu-enkephalin lysine **(SEQ ID NO:50)** and met-enkephalin lysine **(SEQ ID NO:49)**. The amino acid side chain of the lysine is preferably utilized in bonding.--

At page 13, lines 18-22:

--In another aspect, the amphiphilic drug-oligomer conjugates moieties are configures as follows:

R-$OCH_2CH_2OCH_2CH_2C(O)OCH_2CH_2CH_2OCH_2CH_2CH_2NH$-Enkepahlin (**SEQ ID NO:1**); or

R-$OCH_2CH_2OCH_2C(O)OCH_2CH_2NH$-Enkephalin (**SEQ ID NO:1**).

Wherein R=$alkyl_{1\text{-}26}$, cholesterol or amantane.--

At page 17, lines 5-6:

--3.2 FIGURE 2: Compares the stability of the cetyl-PEG2-enkephalin-lys (**SEQ ID NO:1**) conjugate (non-hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:48**) in rat brain homogenate.--

At page 17, lines 7-8:

--3.3 FIGURE 3: Compares the stability of the cetyl-PEG3-enkephalin (**SEQ ID NO:1**) conjugate (non-hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:47**) in rat brain homogenate.--

At page 17, lines 9-10:

--3.4 FIGURE 4: Compares palmitate-PEG3-Enk (**SEQ ID NO:1**) conjugate (hydrolyzable) to unconjugated enkephalin (**SEQ ID NO:47**) in rat brain homogenate.--

A13

At page 17, lines 13-14:

--3.6 FIGURE 6: Graph demonstrating competitive binding between cetyl-PEG_2-enkephalin (**SEQ ID NO:1**) conjugate and naloxone, an Opioid μ receptor agonist.--

A14

At page 17, lines 15-16:

--3.7 FIGURE 7: Graphic comparison of analgesic effect of cetyl-PEG_2-enkephalin (**SEQ ID NO:1**) with clonidine (a morphine substitute).--

A15

At page 18, lines 11-17:

--The amphiphilic oligomers are composed of lipophilic and hydrophilic moieties. The lipophilic moieties are preferably natural fatty acids or alkyl chains. The hydrophilic moieties are preferably small segments of PEG, having 1 to 7 PEG moieties, and preferably having 1 to 5 PEG moieties. The length and composition of the lipophilic moieties and the hydrophilic moieties may be adjusted to obtain desired amphiphilicity. For example, the carbon chains of the fatty acid or alkyl moieties may be lengthened to increase lipophilicity, while PEG moieties may be lengthened to increase hydrophilicity.--

A16

At page 20, lines 1-3:

--The covalent bond between the oligomer and the drug is preferably amide (a carboxy group of the oligomer is linked to an amine group of the peptide), or carbamate (a chloroformate group of the oligomer is linked to an amine group of the peptide).--

A17

At page 20, lines 4-10:

--For non-peptide drug, the bond is preferably ester (a carboxy group of the drug is covalently coupled to a hydroxyl group of the oligomer or a carboxy group of the oligomer is covalently coupled to a hydroxyl group of the drug), amide (a carboxy group of the oligomer is linked to an amine group of the drug) or carbamate (a chloroformate group of the oligomer is linked to an amine group of the drug). For the enkephalin analogues, the preferred peptides are leu-enkephalin lysine **(SEQ ID NO:50)** and met-enkephalin lysine **(SEQ ID NO:49)**. The amino residue of the lysine is preferably utilized in bonding.--

At page 20, line 24-27:

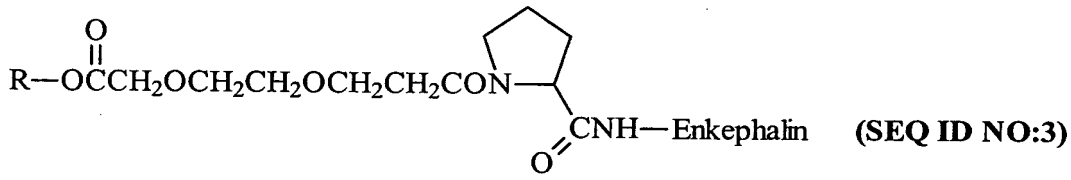
--In another aspect, the oligomer is attached to the C-terminus of the peptide drug. For example:

R-$OCH_2CH_2OCH_2C(O)OCH_2CH_2CH_2OCH_2CH_2CH_2NH$-Enkepahlin **(SEQ ID NO:1)**; or

R-$OCH_2CH_2OCH_2C(O)OCH_2CH_2NH$-Enkephalin **(SEQ ID NO:1)**.--

At page 21, lines 2-9:

--In another aspect, the oligomer is attached at the N-terminus of the peptide drug. For example:



(SEQ ID NO:3)

(SEQ ID NO:3)

It will be appreciated by one of skill in the art that the oligomers may be attached at the carboxy terminus or at a constituent of an amino acid side chain, such as a the amino group of lysine.--

At page 24, lines 10-15:

--While the description is primarily and illustratively directed to the use of enkephalin as a peptide component in various compositions and formulations of the invention, it will be appreciated that the utility of the invention is not thus limited, but rather extends to any peptide species which is capable of conjugation to the oligomers herein described, or which is capable of being modified, as for example by the incorporation of a proline residue, so as to enable the peptide to be conjugated to the oligomers described herein.--

021

At page 24, line 28 through page 25, line 11:

--In another aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,641,861, which is incorporated herein by reference, so long as any of such peptides contains a lysine residue. Exemplary peptides described therein include: Ac-Phe-Arg-Trp-Trp-Tyr-Lys—NH_2 **(SEQ ID NO:4)**; Ac-Arg-Trp-Ile-Gly-Trp-Lys—NH_2 **(SEQ ID NO:5)**; Trp-Trp-Pro-Lys-His-Xaa—NH_2 **(SEQ ID NO:6)**, where Xaa can be any one of the twenty naturally occurring amino acids, or Trp-Trp-Pro-Xaa—NH_2 **(SEQ ID NO:7)**, where Xaa is Lys or Arg; Tyr-Pro-Phe-Gly-Phe-Xaa—NH_2 **(SEQ ID NO:8)**, wherein Xaa can be any one of the twenty naturally occurring amino acids; (D)Ile-(D)Met-(D)Ser-(D)Trp-(D)Trp-Gly_n-Xaa—NH_2 **(SEQ ID NO:9)**, wherein Xaa is Gly or the D-form of a naturally-occurring amino acid and n is 0 or 1, peptides of this formula can be hexapeptides when Gly is absent (n is 0) and heptapeptides when Gly is present (n is 1); (D)Ile-(D)Met-(D)Thr-(D)Trp-Gly-Xaa—NH_2 **(SEQ ID NO:10)**, wherein Xaa is Gly or the D-form of a naturally-occurring amino acid; Tyr-A1-B2-C3—NH_2 **(SEQ ID NO:11)**, wherein A1 is (D)Nve or (D)Nle, B2 is Gly, Phe, or Trp, and C3 is Trp or Nap; Pm and red {Me_xH_yN-Tyr-$(NMe)_z$-Tyr-Xaa_z—NH_2} **(SEQ ID NO:12)**, wherein x and y independently are 0,1, or 2 and z is 0 or 1, and wherein Xaa is Phe, D-Phe, or NHBzl; Trp-Trp-Pro-D4-His_z-Xaa_z-NH_2 **(SEQ ID NO:13)**, wherein z is 0 or 1, D4 is Lys or Arg and Xaa is any one of the naturally-occurring amino acids.--

022

At page 25, lines 12-26:

--In still another aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,602,099, which is incorporated herein by reference. with the proviso that the conjugation can occur only where there is a free carboxyl or free N-terminal. Exemplary peptides include: H-Tyr-Tic-Phe-Phe-OH **(SEQ ID NO:14)**; H-Tyr-Tic-Phe-Phe-NH_2 **(SEQ ID NO:15)**; Tyr(NαMe)-Tic-Phe-Phe-OH **(SEQ ID NO:16)**; Tyr(NαCpm)-Tic-Phe-Phe-OH **(SEQ ID NO:17)**; Tyr(NαHex)-Tic-Phe-Phe-OH **(SEQ ID NO:18)**; Tyr(NαEt_2)-Tic-Phe-Phe-OH **(SEQ ID NO:19)**; H-Dmt-Tic-Phe-Phe-OH **(SEQ ID NO:20)**; H-Dmt-Tic-Phe-Phe-NH_2 **(SEQ ID NO:21)**; H-Tyr(3-F)-Tic-Phe-Phe-OH **(SEQ ID NO:22)**; H-Tyr(3-Cl)-Tic-Phe-Phe-OH **(SEQ ID NO 23)**; H-Tyr(3-Br)-Tic-Phe-Phe-OH **(SEQ ID NO:24)**; H-Dmt-TicΨ[CH_2—NH]Phe-Phe-OH **(SEQ ID NO:25)**; H-Dmt-TicΨ[CH_2—NH]Phe-Phe-NH_2 **(SEQ ID NO:26)**; H-Tyr-TicΨ[CH_2—NCH_3]Phe-Phe-OH **(SEQ ID NO:27)**; H-Tyr-TicΨ[CH_2—NH]Hfe-Phe-OH **(SEQ ID NO:28)**; Tyr(NMe)-TicΨ[CH_2—NH]Hfe-Phe-OH[)] **(SEQ ID NO:29)**; H-Tyr-Tic-Phg-Phe-OH **(SEQ ID NO:30)**; H-Tyr-Tic-Trp-Phe-OH **(SEQ ID NO:31)**; H-Tyr-Tic-Trp-Phe-NH_2 **(SEQ ID NO:32)**; H-Tyr-Tic-His-Phe-OH **(SEQ ID NO:33)**; H-Tyr-Tic-2-Nal-Phe-OH **(SEQ ID NO:34)**; H-Tyr-Tic-Atc-Phe-OH **(SEQ ID NO:35)**; H-Tyr-Tic-Phe-Phe(pNO_2)-OH **(SEQ ID NO:36)**; H-Tyr-Tic-Trp-Phe(pNO_2)-OH **(SEQ ID NO:37)**; H-Tyr-Tic-Phe-Trp-NH_2 **(SEQ ID NO:38)**; H-Tyr-Tic-Phe-Phe-Val-Val-Gly-NH_2 **(SEQ ID NO:39)**; H-Tyr-Tic-Phe-Phe-Tyr-Pro-Ser-NH_2 **(SEQ ID NO:40)**; H-Tyr-Tic-Trp-Phe-Tyr-Pro-Ser-NH_2 **(SEQ ID NO:41)**; H-Tyr-Tic-Trp-Phe (pNO_2) -Tyr-Pro-Ser-NH_2 **(SEQ ID NO:42)** and H-Tyr-Tic-Phe-Phe-Leu-Nle-Asp-NH_2 **(SEQ ID NO:43)**.--

At page 25, line 27 through page 26, line 8:

--Abbreviations in the aforementioned peptides of U.S. Patent 5,602,099 may be interpreted as follows: Aib=α-aminoisobutyric acid; Atc=2-aminotetralin-2-carboxylic acid; Boc=tert-butoxycarbonyl; Cpm=cyclopropylmethyl; DCC=dicyclohexyl-carbodiimide; DIEA=diisopropylethylamine; Dmt=2,6-dimethyltyrosine; Et=ethyl; Hex=hexyl; Hfe=homophenylalanine; HOBt=1-hydroxybenzotriazole; MVD=mouse vas deferens; 1-Nal=3-(1'-naphthyl)alanine; 2-Nal=3-(2'-naphthyl)alanine; Phe(pNO_2)=4-nitrophenylalanine; Phg=phenylglycine; Tic=1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; TIP=H-Tyr-Tic-Phe-OH **(SEQ ID NO:44)**; TIP-NH_2=H-Tyr-Tic-Phe-NH_2 **(SEQ ID NO:45)**; TIP(Ψ)=H-Tyr-TicΨ[CH_2-NH]Phe-OH **(SEQ ID NO:46)**; TIPP=H-Tyr-Tic-Phe-Phe-OH **(SEQ ID NO:14)**; TIPP-NH_2=H -Tyr-Tic-Phe-Phe-NH_2 **(SEQ ID NO:15)**; TIPP(Ψ)=H-Tyr-TicΨ[CH_2-NH]Phe-Phe-OH **(SEQ ID NO:47)**; Tyr(3-Br)=3-bromotyrosine; Tyr(3-Cl)=3-chlorotyrosine; Tyr(3-F)=3-fluorotyrosine; and Tyr(NαMe)=Nα-methyltyrosine.--

A24

At page 26, lines 18-20:

--Particularly preferred peptides are endogenous and synthetic Opioid peptides such as the enkephalins. A particularly preferred Opioid is [Met^5]Enkephalin (Tyr-Gly-Gly-Phe-Met) **(SEQ ID NO:48)**.--

A25

At page 27, lines 16-24:

--In addition to the above types of modifications or substitutions, a mimic of one or more amino acids, otherwise known as a peptide mimetic or peptidomimetic, can also be used. As used herein, the term "mimic" means an amino acid or an amino acid analog that has the same or similar functional characteristics of an amino acid. Thus, for example, a (D)arginine analog can be a mimic of (D)arginine if the analog contains a side chain having a positive charge at physiological pH, as is characteristic of the guanidinium side chain reactive group of arginine. A peptide mimetic or peptidomimetic is an organic molecule that retains similar peptide chain pharmacophore groups as are present in the corresponding peptide.--

A26

At page 27, lines 25-30:

--The substitution of amino acids by non-naturally occurring amino acids and peptidomimetics as described above can enhance the overall activity or properties of an individual peptide based on the modifications to the side chain functionalities. For example, these types of alterations can be employed along with the amphiphilic oligomers of the present invention to further enhance the peptide's stability to enzymatic breakdown and increase the peptide's biological activity.--

At page 40, line 6:

--5.2 CONJUGATION OF COMPOUND 2 & 4 WITH [MET-ENKEPHLIN] MET-ENKEPHALIN--

At page 40, lines 14-20:

--To a stirring solution of met-enkephalin **(SEQ ID NO:48)** (0.130 g; 0.1854 mmol) in 5mL of DMF-DCM (2:1) was added TEA (25 µL). The reaction mixture was cooled to 10°C and a solution of palmityl-teg-nsu or cetyl-teg-nsu dissolved in 1mL of DCM was added in one portion. The reaction mixture was stirred for 2h at 10°C. The solvent was removed under reduced pressure and the residue was redissolved in dry ethyl acetate. After evaporation of the solvent 0.310g conjugated enkephalin was obtained. HPLC showed mono & diconjugate oin the ratio of 3:1.--

At page 41, lines 1-9:

--To a suspension of NaH (4.00g; 0.1 mol) in dry THF (300 mL) at 10°C was added diethylene glycol in one portion. The cooling bath was removed and reaction mixture was stirred at room temperature for 2h. At the end the reaction mixture was cooled to 10°C and bromohexadecane (29g; 0.095 mol) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature for 4h. The solvent was removed under reduced pressure and crude was admixed with water and extracted with ethyl acetate (30 mL x 3). The combined organic extract was sequentially washed with water, brine, dried over $MgSO_4$ and evaporated to leave white solid powder, single spot on TLC and single molecular ion peak.--

At page 41, lines 11-15:

--To a cold stirring solution of phosgene (10.0mL; 20% solution in toluene) under nitrogen, a solution of cetyl-PEG_2-OH (1.3g; 4.00 mmol) in dry dichloromethane (5mL) was added. The reaction mixture was stirred at 0°C for 1hr and 2h at room temperature. Excess of phosgene was distilled off using water aspirator, passing through cold solution of dilute NaOH.--

At page 41, lines 16-20:

--The reaction flask was cooled in ice bath and equimolar quantity of triethyl amine and a solution of hydroxy succinimide, dissolved in minimum quantity of THF was added slowly. The reaction mixture was stirred at room temperature for 12h. The solvent was removed completely at 25°C and residue was redissolved in ethyl acetate, washed with water, brine, dried over $MgSO_4$ and evaporated to give pure succinimidyl derivative.--

At page 41, lines 24-25:

--5.4 CONJUGATION OF SUCCINIMIDYL CETYL-PEG2 WITH BOC-LEU...ENK...LYS-OH (SEQ ID NO:51)--

At page 42, lines 1-3:

--Boc-Leu...enk...Lys-OH **(SEQ ID NO:51)** (100mg; 0.125 mmol) was dissolved in 5 mL of DMF:DCM(1:1) and stirred at 10°C under nitrogen. To this clear solution TEA (17.5 µL) and a solution of succinimidyl cetyl-PEG_2, dissolved in 1 mL of DCM were added.--

At page 42, lines 8-9:

--5.4.1 PURIFICATION OF DERIVATIZED BOC-LEU...ENK...LYS-OH (SEQ ID NO:51) ON SILICA GEL COLUMN--

At page 42, lines 10-13:

--The derivatized blocked enkephalin was purified on silica gel column using methanol-chloroform (5% methanol-chloroform) mixture as an eluting solvent. After evaporation of desired fraction 100 mg pure compound was obtained. A product yield of 100 mg was obtained after removal of the solvent.--

At page 42, lines 14-19:

--5.4.2 DEBLOCKING OF BUTYLOXYCARBONYL GROUP FROM DERIVATIZED LEU...ENK (SEQ ID NO:52)

Derivatized Boc-Leu...enk **(SEQ ID NO:52)** (100 mg; 0.0866 mmol) was treated with 0.4ml of TFA-DCM (1:1) for 30 min. at room temperature. The solvent was removed under reduced pressure. The solid was redissolved in 2 mL of methanol, filtered and evaporated; 80 mg of pure product was obtained.--

At page 42, line 23 through page 43, line 10:

--One-hundred milligrams of enkephalin (100 mg; 0.142 mmol) was dissolved in dry dimethylformamide (5 mL) at room temperature. P-nitrophenol or N-hydroxysuccinimide activated (carbonate or ester) of amphiphilic oligomer (1.1 mole equivalent) was dissolved in 1 mL tetrahydrofuran and added to above solution and stirred at room temperature over 1.5 hours. The extent of the reaction was monitored by a reverse phase (C-18) HPLC using isopropanol/water (0.1% trifluoroacetic acid) gradient system. Reaction mixture was evaporated under reduced pressure and the contents were dissolved in an isopropanol-water mixture. This mixture was purified on a 22 mm preparative HPLC column (C-8) with a solvent gradient system made of either isopropanol/water (0.1% trifluoroacetic acid) or acetonitrile/water (0.1% trifluoroacetic acid to give pure monoconjugated and diconjugated enkephalins. The solvent was evaporated at low temperature (<20°C) to give dry produce. The purity of the product was analyzed by reverse phase analytical HPLC, and the MW information was obtained by MALDI (TOF)-mass spectral technique.--

At page 43, lines 17-24:

--Above residue was dissolved in chloroform (50 mL) and to this was added cholesterol (1.05 mole equivalent) in chloroform (50mL) and triethylamine (1 mole equivalent) over 30 minutes at 5°C. The reaction was stirred at 15°C over 2 hours. To this was added N-hydroxysuccinimide (1 mole equivalent) in chloroform (50mL) and followed by triethylamin (1 equivalent) at 5°C and allowed to stir overnight. Solvent was stripped off and the product was extracted with ethylacetate. Crude product was purified on a silica gel column with 1:10 methanol/chloroform solvent system to obtain activated amphiphilic oligomer in 80% yield.--

At page 44, lines 5-6:

--5.7 STABILITY OF MET ENKEPHALIN-LYS (SEQ ID NO:49) (ENKEPHALIN) AND ITS AMPHIPHILIC OLIGOMER CONJUGATES IN RAT BRAIN HOMOGENATE--

At page 44, lines 6-10:

--Met enkephalin-lys **(SEQ ID NO:49)** and its conjugates (Cetyl-PEG_2, Cetyl-PEG_3 and Palmitate-PEG_3) were incubated in 2% rat brain homogenate. Samples were drawn over time intervals and the amount of the substance remaining was measured by a HPLC method. Following experimental procedure was used for the study.--

At page 44, line 11-20:

--Procedure: A 2% rat brain homogenate was prepared by homogenizing freshly perfused (PBS buffer) rat brain in PBS buffer (pH 7.4). Two 3-mL aliquots of the homogenate were equilibrated at 37°C in a water bath. To one unmodified enkephalin was added to other modified (conjugate) was added, resulting in a final concentration of 60 μg/mL of peptide. At time 0, 1, 2, 3, 5, 15, 30, and 60 minutes, 200 μL of aliquot was withdrawn and quenched with 200 μL of the quenching agent (1% trifluoroacetic acid in acetonitrile/isopropanol or 1% trichloroacetic acid in water). The sample solutions were vortexed and centrifuged at 7000RPM. The supernatant was analyzed by a HPLC method using a gradient of 10 to 100% isopropanol/water (0.1% trifluoroacetic acid) on a C-18 column.--

At page 44, line 21 through page 45, line 2:

--Figure 2 shows the stability of the cetyl-PEG_2-enkephalin **(SEQ ID NO:1)** conjugate as compared to free met-enkephalin-lys **(SEQ ID NO:49)**. Figure 3 shows the stability of the cetyl-PEG_3-enkephalin **(SEQ ID NO:1)** as compared to met-enkephalin-lysine **(SEQ ID NO:49)**. Figure 4 shows palmitate-PEG_3-enk **(SEQ ID NO:1)** (hydrolyzable) conjugate as compared to met-enkephalin-lys **(SEQ ID NO:49)**.--

At page 45, lines 6-7:

--The following procedure was used to identify the presence of conjugate from the brain specimen of animals dosed with 5 mg/kg cetyl-PEG_2-enkephalin **(SEQ ID NO:1)**.--

At page 45, lines 8-19:

--After 10 minutes of dosing, the brain of the animal was perfused with 1.5% trifluoroacetic acid in PBS solution, and the brain was removed and frozen at -70 °C. The brain was homogenized with 1mL of 1.5% trifluoroacetic acid in PBS solution and the homogenate was extracted with acetonitrile/isopropanol solution. The extract was treated with saturated sodium chloride solution and frozen at -20°C for 2 hours.. The organic layer was isolated and centrifuged at 4000RPM. The supernatant was evaporated and the resulting residue was reconstituted in acetonitrile/isopropanol/water mixture. The reconstituted solution was analyzed by HPLC using a gradient of 10 to 100% isopropanol/water (0.1% trifluoroacetic acid) on a C-18 column. The presence and the concentration of cetyl-PEG_2-enkephalin (**SEQ ID NO:1**) conjugate in the extract were measured by comparing the retention time and the peak area of standard solution under the same analytical condition. The results are presented in FIGs 5A to 5D.--

At page 45, lines 21-25:

--The results demonstrate that monoconjugates were isolated from brain tissue. FIG 5A shows a peak produced by cetyl enkephalin (**SEQ ID NO:1**) standard, while 5B shows a corresponding peach demonstrating that cetyl enkephalin (**SEQ ID NO:1**) was actually present in the brain extract. In contrast, neither the vehicle (FIG. 5C) nor the unconjugated enkephalin (**SEQ ID NO:49**) (FIG. 5D) showed a corresponding peak.--

At page 46, lines 8-14:

--Met-enkephalin-lys **(SEQ ID NO:49)** and met-enkephalin-lys derivatives **(SEQ ID NO:1)** were assessed for analgesic activity by rat paw-hot plate assay. Rats were given an injection of naloxone at 0.5 mg/kg (s.c.) then administered a single administration of cetyl-enkephalin **(SEQ ID NO:1)** by the tail vein 10 minutes later at a dose of 5.0 mg/kg. The results as graphically displayed in FIG. 6 demonstrate that Naloxone, an μ-receptor antagonist prevents competitively inhibits binding of cetyl-PEG_2-enkephalin **(SEQ ID NO:1)**, thus demonstrating that at least part of the activity of cetyl-PEG_2-enkephalin **(SEQ ID NO:1)** is attributable to binding at the Opioid μ-receptor.--

At page 46, lines 15-16:

--In a separate study, rats were administered cetyl-enkephalin **(SEQ ID NO:1)** (5.0 mg/kg, i.v.) or clonidine (0.125 mg/kg, i.v.).--

At page 46, line 26 through page 47, line 4:

--The results are displayed in the following tables and in the Graph of FIG 6. The results demonstrate that while 20 mg/kg enkephalin **(SEQ ID NO:49)** alone has 0% analgesic effect as compared to morphine as a baseline, the enkephalin conjugates of the present invention had strong analgesic effects and one conjugate, DHA-PEG-ENK **(SEQ ID NO:1)** had 130% of the analgesic effect of morphine. The graph of FIG. 7 shows that CETYL-PEG-ENK **(SEQ ID NO:1)** produces a response and duration comparable to that of clonidine, an α-andrenergic receptor agonist.--

At page ~~46~~ 47, please replace the table with the following table:

ANALGESIC EFFECT OF ENKEPHALIN CONJUGATES IN RATS				
Drug or Conjugate	**Dose (mg/kg)**	**Number of Rats**	**Mean Analgesia as Compared with Morphine at 3 mg/Kg***	
			@ 5 min	**@ 30 min**
Morphine	3	8	100%	100%
Enkephalin **(SEQ ID NO:49)**	20	7	0%	0%
Cetyl-PEG-ENK **(SEQ ID NO:1)**	5	8	84%	75%
DHA-PEG-ENK **(SEQ ID NO:1)**	20	8	130%	67%
Cholesterol-PEG-ENK **(SEQ ID NO:1)**	5	8	80%	68%
Linolenic-PEG-ENK **(SEQ ID NO:1)**	10	8	77%	73%

At page 48, lines 1-22:

--Agonist-stimulated [^{35}S]GTPγS autoradiography was performed as described by Sim *et al. Proc. Nat'l Acad. Sci.* USA1992 Pg. 7242 - 7246. Animals were sacrificed by decapitation and brains were removed and frozen in isopentane at -30°C. Coronal and horizontal brain sections were cut on a cryostat maintained at -20°C. Sections were incubated in assay buffer (50 mM Tris-HCl, 3 mM $MgCl_2$, 0.2 mM EGTA, 100 mM NaCl, pH 7.4) at 25°C for 10 min. Sections were then incubated in assay buffer containing 2 mM GDP, protease inhibitor cocktail (10 µl/ml of a solution containing 0.2 mg/ml each of bestatin, leupeptin, pepstatin A and aprotinin), and adenosine deaminase (9.5 mU/ml) at 25°C for 15 min. Section were then incubated in assay buffer with GDP, 0.04 nM [^{35}S]GTPγS and appropriate agonist at 25°C for 2 hours. The agonists were: 10 µM DAMGO, 10 µM cetyl-enkephalin **(SEQ ID NO:1)** and 10 µM cetyl-TEG-enkephalin **(SEQ ID NO:1)**. Basal binding was assessed in the absence of agonist. Slides were rinsed twice for 2 min each in cold Tris buffer (50 mM Tris-HCl, pH 7.4) and once in deionized H_2O. Slides were dried overnight and exposed to film for 72 hours. Films were digitized with a Sony XC-77 video camera and analyzed using the NIH IMAGE program for Macintosh computers.

5.9.3 RESULTS

Results show that cetyl-TEG-enkephalin **(SEQ ID NO:1)** stinulates of [^{35}S]GTPγS binding. The anatomical distribution of the binding is consistent with that of µ Opioid receptors. These results demonstrate that cetyl-TEG-enkephalin **(SEQ ID NO:1)** does not simply bind the receptor but also activates the receptor, causing the receptor to bind to G-protein. This activation provides further corroborative evidence that cetyl-TEG-enkephalin **(SEQ ID NO:1)** directly stimulates analgesia.--